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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,984	CHEN ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/24/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6,9-19, 21-28-35,37-47, and 49-84* is/are pending in the application.

4a) Of the above claim(s) *21-27 and 49-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6,9-19,28-35,37-47 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4, 5, 7, 8, 20, 36 and 48 have been cancelled. Claims 21-27 and 49-83 are withdrawn. Claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 are under examination. Applicant's amendment, for example claim 6, has necessitated a new ground of rejection. Accordingly, this action is FINAL.

Withdrawn rejections:

Applicant's amendments and arguments filed 4/24/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brodbeck et al. (US 6,331,311) in view of Brodbeck et al. (6,130,200), and Penco et al. (Polymer International 1998, 46, 203-216) and Ravivarapu et al. (European Journal of Pharmaceutics and Biopharmaceutics 50 (2000)263-270).

Applicant claims an injectable gel composition comprising a plurality of bioerodible, biocompatible polymers, solvent and a beneficial agent.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Brodbeck et al. teach an injectable depot gel composition comprising a biocompatible polymer such as lactic acid based polymers with a number average molecular weight of from 1,000 to 120,000, an organic solvent and a beneficial agent dispersed in the gel (Abstract and claims 1-3 and 5). Claims 1-3 are reproduced below for Applicant's benefit (examiner added emphasis):

1. An injectable depot gel composition comprising:
a continuous, viscous gel phase comprising
a biocompatible polymer and
an organic solvent that dissolves the biocompatible polymer and forms a viscous gel;
a beneficial agent; and a separate, droplet phase dispersed in the viscous gel phase comprising
an emulsifying agent, whereby the depot gel composition is thixotropic.

2. The injectable gel depot composition of claim 1 wherein the biocompatible polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly (malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and mixtures thereof.

3. The injectable depot gel composition of claim 1 wherein the biocompatible polymer is a lactic acid-based polymer.

Claim 4 recites the lactic acid based polymer has a monomer ratio of lactic acid to glycolic acid in the range of 100:0 to about 15:85 (claim 4). Clearly, Brodbeck et al. contemplate the use of biodegradable and biocompatible lactic acid based polymers. Furthermore, Brodbeck et al. teach mixtures of the lactic acid based polymers in the molecular weight range of from 1000 to 120,000 (claim 5). Thus, one interpretation of the claims is that Brodbeck et al. teach mixtures of lactic acid based polymers of a wide molecular weight range. This would include low, medium and high molecular weight polymers in the range of claim 5. Brodbeck et al. teach the solvent is present from 20 to 95 % by weight of the combined amounts of polymer and solvent (Claim 10). Therefore the polymer must be from 5 to 80 % by weight of the composition. '311

teaches benzyl benzoate, an aromatic ester, as a solvent (column 5, lines 8-15) and alcohols, polyols, esters, carboxylic acids, ketones, aldehydes and mixtures thereof as emulsifying agents (claims 19). Brodbeck et al. teach prolonged release of the beneficial agent up to 90 days and modifying the release by adjusting the amounts of components for any given polymer and any given solvent (column 7, line 35 bridging column 8, line 53). Brodbeck et al. teach a kit for the injectable depot composition with the components (a) a biocompatible polymer and organic solvent; (b) emulsifying agent and (c) the beneficial agent (claim 27). The beneficial agent is thus separated from the solvent and mixed before use (column 8, lines 53-61). (Note: components (d)-(g) are optional in instant claim 84).

Brodbeck et al. '200 teach a gel composition for implantation of a beneficial agent to a subject comprising a biocompatible polymer, a biocompatible solvent with low water miscibility that forms a gel with the polymer and a beneficial agent (Abstract). Brodbeck et al. '200 teach poly(lactide-co-glycolide) copolymer, benzyl benzoate and a beneficial agent (Claims 1-3) wherein the copolymer has a number average molecular weight of from 1,000 to 120,000 (claim 15). A component solvent can be added such as diethyl phthalate (claim 17). Brodbeck et al. '200 teach that useful solvents are less than 7% water soluble by weight (column 12, lines 12-65). Brodbeck et al. '200 teach the use of RESOMER® RG502 AND RESOMER® RG503 for use in the invention (column 24, line 46 bridging column 25, line 5).

Penco et al. teach benzyl alcohol as a known solvent for PLGA (page 204-205, 2. synthesis).

Ravivarapu et al. teach, in the Abstract, *the concept* combining PLGA polymers that varied in their molecular weights in various ratios yielded microspheres with varied drug release

profiles commensurate with the hydration tendencies of the polymers. Increasing the component of lower molecular weight 50:50 hydrophilic PLGA polymer, 8.6 kDa increased the initial drug release. A.similar microsphere formulation prepared instead with blending microspheres from individual polymers showed a similar increase. In an animal model, microspheres obtained from polymer or microsphere blends attained a faster onset of testosterone suppression as compared to microspheres from higher molecular weight 50:50 hydrophilic PLGA polymer, 28.3 kDa, alone. Ravivarapu et al. explain on page 268, right column (examiner added emphasis):

and during the 14–49 day period. PLGA polymers degrade hydrolytically giving rise to an acidic microenvironment in the particle structure [21] which enhances polymer degradation and mass loss. An acidic microenvironment is attained faster in the case of the 8.6 kDa PLGA as this polymer hydrates faster owing to its higher number of carboxylic acid endgroups. Additionally, microspheres from the lower MW polymer had a more porous internal structure which would also facilitate hydration. Thus, microspheres that contain 8.6 kDa PLGA as a combination in their structure are expected to degrade and release drug faster as compared to microspheres that are physically blended, as the hydration of the 8.6 kDa polymer will also hydrate the closely associated 28.3 kDa polymer. This may explain the higher drug release seen with polymer combination formulations at later time points. However, as the noted difference

These studies illustrated the concept of blending polymers or microspheres of varied characteristics in achieving modified drug release. It is then understood by one of ordinary skill in the art that low MW PLGA degrades faster and results and faster drug release while higher MW PLGA degrades more slowly thus manifesting a slower drug release and mixtures of the different MW polymers produces a blended release profile.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant invention and Brodbeck et al. '311 is that Brodbeck et al '311 does not expressly teach mixtures of high, medium and low molecular weight lactic acid based polymers in the injectable drug depot wherein the low molecular weight polymer is about 20 to about 90 wt%. This deficiency is cured by the teachings of Brodbeck et al '200 and Ravivarapu et al..

2. The difference between the instant invention and Brodbeck et al '311 is that Brodbeck et al '311 does not expressly teach benzyl alcohol as a solvent. This deficiency in Brodbeck et al'311 is cured by the teachings of Penco et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a mixture of high, medium and low biocompatible lactic acid based

polymers as taught by Brodbeck et al '311 and use for example the lactic acid based polymers RESOMER® RG502 AND RESOMER® RG503, as suggested by Brodbeck et al '200, and in various molecular weights, as taught by Ravivarapu et al., in the gel depot of Brodbeck et al '311 and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because '311 teaches one of ordinary skill in the art mixtures of polylactides and copolymers thereof and teaches a wide range of molecular weights that encompass the instantly claimed high, medium and low molecular weight ranges that can be used to make the injectable drug depot gel composition. Ravivarapu et al. teach the benefits of combining polymers/microspheres of different molecular weights to achieve different active release profiles. It is then merely routine optimization and judicious selection of known components in the art, for example RESOMER® RG502 AND RESOMER® RG503, for use in the composition especially when Brodbeck et al '200 teaches use of these materials for the same purpose. With respect to the limitation of systemic delivery of the beneficial agent over a duration of one year or local delivery of the beneficial agent over a duration of up to one year, that is merely routine optimization, as taught by Brodbeck et al '311, of the components to arrive at that desired release profile.

Regarding the relative amount of low molecular weight polymer of about 20 to about 90 wt% in the matrix recited in Applicants' dependent claims; the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired

results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use benzyl alcohol, as taught by Penco et al., as the solvent in the composition of Brodbeck et al '311 and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because benzyl alcohol is a known solvent for PLGA polymers as taught by Penco et al. Benzyl alcohol intrinsically has the properties of water miscibility instantly claimed in the absence of evidence to the contrary (see instant claims 12-15 and 40-43).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant disagrees that the language in Brodbeck instructs the skilled person to select mixtures of lactide polymers having different molecular weights and asserts that claim 5 of

Brodbeck instructs the use of a single "lactic acid-based polymer" not polymers and that the Office has based its rejection on a misreading of the Brodbeck claim language. Respectfully, the Examiner cannot agree. The claims in question are:

We claim:

1. An injectable depot gel composition comprising:

a continuous, viscous gel phase comprising

a biocompatible polymer and

an organic solvent that dissolves the biocompatible polymer and forms a viscous gel;

a beneficial agent; and a separate, droplet phase dispersed in the viscous gel phase comprising

an emulsifying agent, whereby the depot gel composition is thixotropic.

2. The injectable gel depot composition of claim 1 wherein the biocompatible polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly (malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and mixtures thereof.

3. The injectable depot gel composition of claim 1 wherein the biocompatible polymer is a lactic acid-based polymer.

4. The injectable depot gel composition of claim 3 wherein the lactic acid-based polymer has a monomer ratio of lactic acid to glycolic acid in the range of 100:0 to about 15:85.

11

5. The injectable depot gel composition of claim 3 wherein the lactic acid-based polymer has a number average molecular weight of from 1,000 to 120,000.

Limiting the disclosure of Brodbeck as Applicant asserts is too narrow an interpretation of Brodbeck. Taken as a whole, clearly Brodbeck teaches a plurality of polylactides in claim 2. This means more than one polylactide. Claim 5 merely teaches the average molecular weight that one of ordinary skill in the art could select for use in the invention. Given that Brodbeck teaches a plurality of polylactides and the molecular weight range to select from for the polylactides, it remains the Examiner's position that this is not an unreasonable interpretation of the reference. Limiting the selection of copolymers from the Markush group of claim 2 of Brodbeck is simply too narrow an interpretation of the art.

Applicant asserts that the skilled person would not look to Ravivarapu in order to improve or modify Brodbeck. Respecfully, the Examiner is relying on Ravivarapu for the concepts provided therein which would be known to a person of ordinary skill in the art of drug delivery systems. Ravivarapu does not teach away as Applicant asserts but rather provides insight on the function of mixed polymer systems for drug delivery.

From MPEP 2143: "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida v. AGPro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson 's-Black Rock,Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969);*Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152,87 USPQ 303, 306 (1950).

In other words, all the elements claimed are known in the art and would be expected to function in the same way. Beneficial agents function as beneficial agents. Solvents function as

solvents. PGLA at low molecular weight functions as PGLA at low molecular weight and high molecular weight PGLA functions as high molecular weight PGLA. All Applicant has done is assemble known elements in the art into one composition. This is relevant to commercial success not invention. The fact that a combination has filled a long-felt want and has enjoyed commercial success will not, without invention, make the combination patentable. (See *ANDERSON'S-BLACK ROCK, INC., Petitioner, v. PAVEMENT SALVAGE CO.*, U.S.P.Q. 673, 396 U.S. 57, 90 S.Ct. 305, 24 L.Ed.2d 258, 163). Applicant has not argued synergy.

Respectfully, Applicant's arguments are not persuasive and the Examiner maintains the rejection.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/

Primary Examiner, Art Unit 1616